Chapter 04

Cell Repair and Wound Healing

REPAIR

Repair is the process by which lost or destroyed cells are replaced by viable cells.

There are two processes of repair:

- Regeneration
- Replacement by connective tissue

Repair by regeneration

The replacement of the destroyed tissue by the parenchymal cells of the same type is called regeneration. In other words, the replacement of destroyed cells by proliferation of surrounding undamaged cells of the same type is called regeneration.

Regenerative capacity of different cell types

The cells of the body are divided into three groups on the basis of their regenerative capacity as following:

Continuously dividing (labile) cells

These cells proliferate throughout life, replacing those cells that are continuously dying.

Examples

- Stratified squamous epithelium of skin, oral cavity, vagina and cervix
- Cuboidal epithelium of the ducts draining exocrine organs e.g. salivary glands, pancreas and biliary tract
- Columnar epithelium of GIT, uterus, and fallopian tubes
- Hematopoietic (blood forming) cells of bone marrow

Quiescent (stable) cells

These cells have the capacity to regenerate, but in normal conditions, do not actively replicate. However, these can undergo rapid division in response to a variety of stimuli and are thus capable of reconstitution of the tissue of origin.

Examples

- Parenchymal cells of liver, kidney and pancreas
- Mesenchymal cells e.g. smooth muscle, cartilage, connective tissue, fibroblast and vascular endothelial cells

Non-dividing (permanent) cells

These cells are incapable of division and regeneration. If they are destroyed, the loss is permanent and repair occurs only by the connective tissue (i.e. by scar formation).

Examples

- Nerve cells (neurons)
- Cardiac muscles
- Skeletal muscles

Control of cell growth

Cellular proliferation is largely regulated by biochemical factors produced in the local micro-environment that can either stimulate or inhibit cells growth. These biochemical factors that stimulate growth are called growth factors while those that inhibit growth are called inhibitory factors.

Growth factors

Cell proliferation is mediated by chemical mediators. The most important chemical mediators are polypeptide growth factors which are circulating in the serum or produced locally by the cells.

- Epidermal growth factor
- Platelet derived growth factor
- Fibroblast growth factor
- Vascular endothelial growth factor
- Cytokines e.g. interleukin-1 and tumor necrosis factors

Inhibitory factors

- Transforming growth factors f3
- Tumor necrosis factors

Repair by connective tissue (scar formation)

Following are the conditions in which tissue repair is achieved by scar formation.

1. When resolution (recovery) fails to occur in an acute inflammation.
2. When parenchymal cell necrosis cannot be repaired by regeneration because
   - Necrotic cells are permanent cells.
   - Stable cells are destroyed.
   - Necrosis is so extensive that no cells are available-for regeneration.

Phases of repair by scar formation

Preparation

The area of injury is prepared for scar formation by removal of the inflammatory exudate by the lymphatics.

Ingrowth of granulation tissue

Granulation tissue forms and fills the injured area while the necrotic debris is being removed. Granulation tissue is highly vascularized connective tissue composed of newly-formed capillaries, proliferating fibroblasts, and residual inflammatory cells. On gross examination, granulation tissue is soft and pink because of numerous capillaries. Microscopic examination shows thin walled capillaries lined by endothelium and surrounded by fibroblasts.

Production of fibronectin

Fibronectin is a glycoprotein that plays key role in the formation of granulation tissue and is present in large amounts during wound healing. In early phases, it is derived from plasma, but later it is synthesized by fibroblasts, macrophages and endothelial cells in granulation tissue.

Collagenization (Fibrosis)

Collagen is the major fibrillary protein of connective tissue. It is synthesized by fibroblast and is responsible for much of the tensile strength of scar tissue. The terms fibrous tissue and scar tissues are synonymous with collagen.

Maturation of scar

A young scar consists of granulation tissue and abundant collagen together with capillaries and fibroblasts. It appears pink on gross examination because of the vascularity. As the scar matures; the amount of collagen increases and the scar becomes less cellular and less vascular. The mature scar is composed of an avascular, poorly cellular mass of collagen, and is white on gross examination.

Contraction and strengthening

It is the final phase of scar formation. Contraction decreases the size of scar and enables the surviving cells of the organ to function with maximum effectiveness.

HEALING OF SKIN WOUNDS

Abrasion

This is the mildest form of skin injury characterized by removal, of the superficial part of the epidermis. Since the underlying basal germinative layer of labile cells is intact, the epithelium regenerates from below, and the integrity of the epithelium is restored with no scarring.

Incision (cut) and laceration (tear)

Incision and lacerations involve the full thickness of the skin (both epidermis and dermis) but with minimal loss of germinative cells. If the skin edges are carefully opposed, as in sutured surgical incision, only a small gap remains to be repaired. This process, in which necrosis and inflammation are minimal, is known as *healing by first intention.*

Wounds with epidermal defects

Severe injuries (e.g. crush injuries, extensive lacerations, burns) are characterized by loss of large areas of the complete epidermis, including the germinative cells. The extensive necrosis that is present in such wounds is accompanied by a phase of inflammation prior to the repair process. This process of healing is known as *healing by second intention.*

Healing mechanisms

- Healing by first intention (healing by primary union)
- Healing by second intention (healing by secondary union)

Healing by first intention

This occurs at a site where there is only minimal loss of tissue such as a clean surgical wound with good opposition of edges.

Stages

- Exudation of blood into the space b/w the cut
- Coagulum drying on its surface and forming scab
- Formation of granulation tissue
- Proliferation of adjacent epithelial cells and migration toward the defect to restore continuity
- Mature fibroblast laying down collagen
- Maturation of collagen and devascularization forming avascular scar

Healing by second intention

This occurs in open wounds particularly when there has been significant loss of tissue with separate edges such as ulcer or abscess cavity. Healing in this type is slow and results in large scar.

Stages

- Cavity fills with blood and fibrin clot (coagulum).
- Coagulum dries on its surface and forms scab.
- Acute inflammation starts at junction of living tissue.
- Wound contraction leads to reducing its size.
- Granulation tissue forms in coagulum.
- Adjacent epithelial cells proliferate and migrate over the granulation tissue beneath coagulum.
- Scar forms from granulation tissue.

Difference between primary and secondary intention repair

Primary

- Occurs when wound edges are in good opposition
- Less formation of inflammatory exudate
- Formation of small amount of granulation tissue
- Small scar formation
- Rapid healing

Secondary

- Occurs when edges are separated
- Excessive inflammatory exudate formation
- Large amount of granulation tissue
- Large scar formation
- Slow healing

Complications of wound healing

1. Infection
2. Dehiscence (bursting of a wound especially of abdomen)
3. *Keloid:* Accumulation of excessive amount of collagen that produces protruding tumorous scar
4. *Proud flesh:* Formation of excessive amount of granulation tissue which protrudes above the level of the surrounding skin and blocks re-epithelization

Factors affecting the healing process

1. Systemic influences
2. Local influences

Systemic influences

Nutrition

Protein deficiency

Proteins are needed for the processes of healing. Methionine (an amino acid) is essential for building up of granulation tissue. In protein deficiency, granulation tissue and collagen production is delayed, resulting in a weak scar.

Vitamin C deficiency

Vitamin C is essential for the synthesis of collagen fibers. In Vitamin C deficiency, fibroblasts produce little collagen therefore, healing is poor and delayed.

Zinc deficiency

Several enzymes required for DNA and RNA synthesis are zinc dependent. The deficiency of zinc impairs DNA and RNA synthesis that leads to impaired wound healing.

Blood derangement

Neutropenia

Decreased number or defective neutrophils in blood increases susceptibility to bacterial infection that hinders the process of repair.

Hemorrhagic diatheses

In this situation, extravagation and accumulation of large amount of blood in the wounded area serves as a good medium for bacteriological growth thus hindering the process of repair.

Anemia

Low plasma protein and immunoglobins in anemia impair healing process.

Diabetes mellitus

In diabetes:

- The neutrophils have very low chemotac and phagocytic capacity.
- Diabetic patient's skin contains high levels of glucose that favors survival of bacteria.
- Diabetics develop arterial disease resulting in inadequate blood supply to the injured area.

Hormones

Adrenal corticosteroids delay wound healing by:

- Depressing inflammatory response through stability of lysosomal membrane
- Blocking production of collagen

Temperature

Wound healing is slow in cold weather while fast in hot weather.

Local infection

Infection in the wound will result in prolonged acute inflammation and local tissue injury, causing delay in wound healing.

Blood supply

Poor blood supply slows healing process.

The causes of poor blood supply are following:

- Atherosclerosis
- Endarteritis obliterates
- Venous thrombosis
- Varicose veins
- Pressure on the vessel

Type of tissue involved

Complete repair occurs only in tissues composed of stable and labile cells. Injury to the tissues composed of permanent cells results in scarring.

Foreign bodies

They stimulate inflammation and impair wound healing.

Immobilization

It helps in healing especially in fracture.

Others

Neoplasia, edema, X-rays and ultraviolet rays hinder the healing process.

Factors that delay wound healing

Systemic

- Protein deficiency
- Vitamin C deficiency
- Zinc deficiency
- Neutropenia
- Hemorrhagic diatheses
- Anemia
- Diabetes mellitus
- Excess corticosteroid
- Advanced age

Local

- Infection
- Poor blood supply
- Presence of foreign material
- Presence of necrotic tissue
- Movement in injured area

1. Factors influencing wound healing are:
   - T a. Infection
   - T b. Blood supply
   - T c. Vitamin C deficiency
   - F d. Vitamin A deficiency
   - T e. Steroids

2. Regeneration is possible in:
   - F a. Brain
   - T b. Liver
   - T c. Epidermis
   - F d. Skeletal and cardiac muscles
   - T e. Smooth muscles

3. Factors predisposing wound infection:
   - T a. Diabetes
   - T b. Foreign bodies
   - T c. Neutropenia
   - F d. Leukocytosis
   - T e. Hypogammaglobinemia

4. Wound healing is enhanced by:
   - T a. Oxygen
   - F b. Cortisol
   - T c. Vitamin C
   - F d. Aldosterone
   - T e. Zinc

5. Following are the characteristics of healing by first intention:
   - T a. Occurs when wound edges are in good opposition
   - T b. Inflammation
   - T c. Formation of granulation tissue
   - T d. Proliferation of adjacent epithelial cells
   - F e. Infection

6. Healing by second intention or healing of open wound is characterized by:
   - T a. Wound edges separated
   - T b. Infection
   - T c. Excessive inflammatory exudate
   - F d. Rapid healing
   - T e. Contraction of the wound characteristic of healing by second intention